

<b>TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371</b>		ATTORNEY'S DOCKET NUMBER <b>P66333US0</b>
		US APPLICATION NO (if known, see 37 CFR 1.5) <b>09 / 762302</b>
INTERNATIONAL APPLICATION NO. <b>PCT/EP99/05724</b>	INTERNATIONAL FILING DATE <b>7 August 1999</b>	PRIORITY DATE CLAIMED <b>12 August 1998</b>
TITLE OF INVENTION <b>ORAL ADMINISTRATION FORM FOR PYRIDIN-2-YLMETHYLSULFINYL-1H-BENZIMIDAZOLES</b>		
APPLICANT(S) FOR DO/EO/US <b>Rango DIETRICH and Hartmut NEY</b>		

Applicant herein submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for Internatl. Preliminary Examination was made by the 19th month from earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
  - a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☒ has been transmitted by the International Bureau.
  - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
  - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
  - b. ☐ have been transmitted by the International Bureau.
  - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
  - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the Internatl. Preliminary Examination report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☒ An assignment document for recording. A separate cover sheet compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.  
☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:

International Search Report - EPO  
 PCT Request Form  
 PCT/IB/304 Form  
 PCT/IB/308 Form  
 First Page of Publication  
 International Preliminary Examination Report - with annexes

US APPLICATION NO. (If known, see 37 CFR 1.5) <div style="font-size: 1.5em; font-weight: bold;">09/762302</div>		INTERNATIONAL APPLICATION NO <div style="font-weight: bold;">PCT/EP99/05724</div>		ATTORNEY'S DOCKET NUMBER <div style="font-weight: bold;">P66333US0</div>					
17. <input checked="" type="checkbox"/> The following fees are submitted:  <b>Basic National Fee (37 CFR 1.492(a)(1)-(5)):</b> Internatl. prelim. examination fee paid to USPTO (37 CFR 1.492 (a) (1)) ... \$690.00 No international preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (2)) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) .. \$710.00 Neither international preliminary examination fee (37 CFR 1.492 (a) (3)) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO) ..... <b>\$1000.00</b> International preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (4)) and all claims satisfied provisions of PCT Article 33(2)-(4) ..... \$100.00 Search Report prepared by the EPO or JPO (37 CFR 1.492 (a) (5)) ..... <b>\$860.00</b> <div style="text-align: right;"><b>ENTER APPROPRIATE BASIC FEE AMOUNT =</b></div>				<table border="1" style="width:100%; border-collapse: collapse;"> <tr> <th style="width:50%;">CALCULATIONS</th> <th style="width:50%;">PTO USE ONLY</th> </tr> <tr> <td style="text-align: right;">\$ 860.00</td> <td></td> </tr> </table>		CALCULATIONS	PTO USE ONLY	\$ 860.00	
CALCULATIONS	PTO USE ONLY								
\$ 860.00									
Surcharge of \$130.00 for furnishing the <b>oath or declaration</b> later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				<table border="1" style="width:100%; border-collapse: collapse;"> <tr> <td style="width:50%; text-align: right;">\$</td> <td style="width:50%;"></td> </tr> </table>		\$			
\$									
<b>Claims</b>	<b>Number Filed</b>	<b>Number Extra</b>	<b>Rate</b>						
Total Claims	19 - 20 =	-0-	x \$18.00	\$					
Independent Claims	1 - 3 =	-0-	x \$80.00	\$					
Multiple Dependent Claim(s) (if applicable)			+ \$270.00	\$					
<b>TOTAL OF ABOVE CALCULATIONS =</b>				\$ 860.00					
Reduction by 1/2, Applicant qualifies for Small Entity Status.				<table border="1" style="width:100%; border-collapse: collapse;"> <tr> <td style="width:50%; text-align: right;">\$</td> <td style="width:50%;"></td> </tr> </table>		\$			
\$									
<b>SUBTOTAL =</b>				\$ 860.00					
Processing fee of \$130 for furnishing the <b>English translation</b> later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f))				<table border="1" style="width:100%; border-collapse: collapse;"> <tr> <td style="width:50%; text-align: right;">\$</td> <td style="width:50%;"></td> </tr> </table>		\$			
\$									
<b>TOTAL NATIONAL FEE =</b>				\$ 860.00					
Fee of \$40.00 for recording the enclosed <b>assignment</b> (37 CFR 1.21(h)). Assignment must be accompanied by appropriate cover sheet (37 CFR 3.28, 3.31).				<table border="1" style="width:100%; border-collapse: collapse;"> <tr> <td style="width:50%; text-align: right;">\$ 40.00</td> <td style="width:50%;"></td> </tr> </table>		\$ 40.00			
\$ 40.00									
<b>TOTAL FEES ENCLOSED =</b>				\$ 900.00					
				Amt. to be refunded:	\$				
				Amt. charged:	\$				
<div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> <p>a. <input checked="" type="checkbox"/> A check in the amount of \$ <u>900.00</u> to cover the above fees is enclosed.</p> <p>b. <input type="checkbox"/> Please charge my Deposit Account No. <u>06-1358</u> in the amount of \$ <u>---</u> to cover the above fees. A duplicate copy of this sheet is enclosed.</p> <p>c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge my account any additional fees set forth in §1.492 during the pendency of this application, or credit any overpayment to Deposit Account No. <u>06-1358</u>. A duplicate copy of this sheet is enclosed.</p> </div> <div style="width: 45%; text-align: right;"> <p>By <u><i>Irwin M. Aisenberg</i></u>              Irwin M. Aisenberg              Reg. No. 19,007</p> </div> </div> <div style="margin-top: 20px;"> <p><b>SEND ALL CORRESPONDENCE TO:</b>  <b>Jacobson, Price, Holman &amp; Stern, PLLC</b>          400 7th Street, N.W., Suite 600          Washington, DC 20004          202-638-6666  <b>CUSTOMER NUMBER: 00136</b></p> </div>									

ORAL ADMINISTRATION FORM FOR PYRIDIN-2-YLMETHYLSULFINYL-1H-BENZIMIDAZOLESSubject of the invention

The present invention relates to a novel oral administration form for pyridin-2-ylmethylsulfinyl-1H-benzimidazoles.

Prior art

Pyridin-2-ylmethylsulfinyl-1H-benzimidazoles and compounds structurally related to these, such as are disclosed, for example, in EP-A-0005129, EP-A-0166287, EP-A-0174726, EP-A-0268956, DE-A-3531487 and EP-A-0434999, have, on account of their H<sup>+</sup>/K<sup>+</sup>ATPase-inhibiting action, considerable importance in the therapy of diseases which are due to increased gastric acid secretion. Examples of active compounds from this group which are commercially available or in an advanced stage of clinical testing are 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: omeprazole), 5-methoxy-2-[(S)-(4-methoxy-3,5-dimethyl-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (prop. INN: esomeprazole), 5-difluoromethoxy-2-[(3,4-dimethoxy-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: pantoprazole), 2-[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl)methylsulfinyl]-1H-benzimidazole (INN: lansoprazole), 2-[4-(3-methoxypropoxy)-3-methylpyridin-2-yl)methylsulfinyl]-1H-benzimidazole (INN: rabeprazole), 2-[2-(N-isobutyl-N-methylamino)benzylsulfinyl]benzimidazole (laminoprazole) and 2-(4-methoxy-6,7,8,9-tetrahydro-5H-cyclohepta[b]pyridin-9-ylsulfinyl)-1H-benzimidazole (nepaprazole).

A common characteristic of the abovementioned pyridin-2-ylmethylsulfinyl-1H-benzimidazoles is the acid sensitivity - which is finally indispensable for their efficacy - of these active compounds, which is seen in their strong tendency to decompose in a neutral and, in particular, acidic environment, strongly colored decomposition products being formed.

In the past, there have been considerable efforts, despite the acid sensitivity of the pyridin-2-ylmethylsulfinyl-1H-benzimidazoles, to obtain stable and storable oral administration forms which contain these compounds. There have likewise been efforts to obtain custom administration forms for pyridin-2-ylmethylsulfinyl-1H-benzimidazoles for certain application purposes.

European Patent EP-B1-244 380 claims an oral administration form for certain pyridin-2-ylmethylsulfinyl-1H-benzimidazoles in which the active compound present in the tablet or pellet core is protected from the gastric acid by an enteric coating, a water-soluble intermediate layer which is intended to protect the core and acidic coating from one another additionally being situated between the active compound core and enteric coating.

09/762302

JC05 Rec'd PCT/PTO 08 FEB 2001

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

Rango DIETRICH et al.

Serial No.: New Application

Filed:

For: ORAL ADMINISTRATION FORM FOR PYRIDIN-2-YIMETHYLSULFINYL-1H-BENZIMIDAZOLES

**PRELIMINARY AMENDMENT**

Assistant Commissioner of Patents  
Washington, D.C. 20231

Dear Sir:

Kindly amend the claims of the above-identified application as follows:

1. (Amended) An oral administration form [for] of an active compound, which is a pyridin-2-ylmethysulfinyl-1H-benzimidazole or a pharmaceutically acceptable salt thereof [and its salts], which comprises the active compound together with a tablet disintegrant[s and is provided with a] in a core which bears a coating film [coating-]customary per se for a sustained [which is] release composition[s].

Claims 8 and 9, line 1 of each, delete "or for combined use with".

Cancel claim 10 without prejudice and insert the following claims in lieu thereof:

--11. A method of treating an amenable disorder of the stomach which comprises administering to a subject in need of such therapy an effective amount of an oral administration form as claimed in claim 1.

12. A method of treating an amenable disorder of the stomach which comprises administering to a subject in need of such therapy an effective amount of an oral administration form as claimed in claim 2.

13. A method of treating an amenable disorder of the stomach which comprises administering to a subject in need of such therapy an effective amount of an oral administration form as claimed in claim 3.

14. A method of treating an amenable disorder of the stomach which comprises administering to a subject in need of such therapy an effective amount of an oral administration form as claimed in claim 4.

15. A method of treating an amenable disorder of the stomach which comprises administering to a subject in need of such therapy an effective amount of an oral administration form as claimed in claim 5.

16. A method of treating an amenable disorder of the stomach which comprises administering to a subject in need of such

therapy an effective amount of an oral administration form as claimed in claim 6.

17. A method of treating an amenable disorder of the stomach which comprises administering to a subject in need of such therapy an effective amount of an oral administration form as claimed in claim 7.

18. A method of treating an amenable disorder of the stomach which comprises administering to a subject in need of such therapy an effective amount of an oral administration form as claimed in claim 8.

19. A method of treating an amenable disorder of the stomach which comprises administering to a subject in need of such therapy an effective amount of an oral administration form as claimed in claim 9.

20. A method of treating an amenable disorder of the stomach which comprises administering an effective amount of an oral administration form as claimed in claim 1 at least substantially concurrently with an administration form of a pyridin-2-ylmethylsulfinyl-1H-benzimidazole having an enteric coating and/or an antimicrobial agent.--

R E M A R K S

Entry of the preceding amendments and favorable action on the merits are respectfully requested.

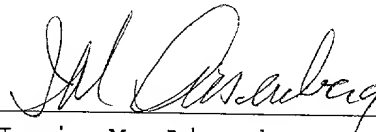
The amendments to claim 1 are entirely editorial in nature and are presented at this time in order to place the claims in better condition for examination and for allowance. Newly presented claims 11 to 19 are based on claim 10 and merely place that claim in condition for examination and avoid having a multiple-dependent claim. Claim 20 is further based on claim 10 and claims 7 to 9. Further support is provided by the final two paragraphs on page 7 and the first paragraph on page 8 of the specification.

Favorable action on the merits is respectfully solicited.

Respectfully submitted,

JACOBSON, PRICE, HOLMAN & STERN, PLLC

By:

  
Irwin M. Aisenberg  
Reg. No. 19,007

400 Seventh Street, N.W.  
Washington, D.C. 20004  
(202) 638-6666  
Atty. Dkt. No.: P66333US0  
IMA/dlj  
Date: February 8, 2001

The protection of the pyridin-2-ylmethylsulfinyl-1H-benzimidazoles from gastric acid by application of an enteric coating can be regarded as the method of choice up to now when oral administration forms for this class of active compound are involved. The enteric coatings, whose resistance to gastric juice is based on the fact that free acidic groups (in particular carboxyl groups) are present in a polymer, must be separated, however, from the acid-sensitive active compound cores by suitable measures. This is carried out by application or production of a protective intermediate layer composed in whatever way (see, for example, EP-B1-589 981, WO-A-9601624, WO-A-9623500, WO-A-9624338, WO-A-9402140, WO-A-9712580 and WO-A-9800115).

### Description of the invention

Surprisingly, it has now been found that an enteric coating for pyridin-2-ylmethylsulfinyl-1H-benzimidazoles is unnecessary if the coating used instead of it is designed so that the active compound is released only after a defined time, namely after gastric passage. Furthermore, it has surprisingly been found that, with a suitable design of the core comprising the active compound, the release of the active compound - once it has commenced - takes place within a short space of time, so that a rapidly rising and high active compound blood level is achieved.

The invention thus relates to an oral administration form for pyridin-2-ylmethylsulfinyl-1H-benzimidazoles and their salts, which comprises the active compound together with tablet disintegrants and is provided with a film coating which is customary per se for sustained-release compositions.

Possible oral administration forms are, for example, pellets, microtablets, minitables or in particular tablets, if desired dispensed in capsules.

Suitable pyridin-2-ylmethylsulfinyl-1H-benzimidazoles within the meaning of the invention are, for example, omeprazole, esomeprazole, lansoprazole, rabeprazole, leminoprazole, nepaprazole and in particular pantoprazole.

Salts of the pyridin-2-ylmethylsulfinyl-1H-benzimidazoles which may be mentioned primarily are the salts with bases, in particular the sodium, potassium, calcium and magnesium salt. The pantoprazole sodium salts, in particular the pantoprazole sodium sesquihydrate, is particularly preferred.

Possible tablet disintegrants are the customary agents known to the person skilled in the art. Examples which may be mentioned are certain cellulose derivatives (e.g. sodium cellulose glycolate and Tyloses), starch, compositions based on sodium carboxymethylcellulose and potato starch (e.g. Primojel), sodium carboxymethylstarch (e.g. Expiotab), bentonite, sodium alginate or pectin, but in particular chemically indifferent agents such as crosslinked polyvinylpyrrolidone (e.g. Crospovidone). The content of tablet disintegrant is customarily between 2 and 10 % by weight based on the entire core. Depending



on the type of tablet disintegrant, however, larger contents can also be used, in the case of Crospovidone, for example, 20-35% by weight.

In addition to the tablet disintegrant, if desired the tablet cores contain further auxiliaries and fillers or binders. Auxiliaries used are, in particular, lubricants and release agents. Mention may be made here, for example, of calcium salts of higher fatty acids, such as, for example, calcium stearate. Binders which may be mentioned are, in particular, polyvinylpyrrolidone and/or hydroxypropylmethylcellulose and, if desired, mannitol, which is additionally preferred as a filler.

To increase the stability of the tablet cores, it has proven advantageous to employ the pyridin-2-ylmethylsulfinyl-1H-benzimidazoles in the form of their salts and/or with addition of one or more physiologically tolerable inorganic compounds having a basic reaction. Mention may be made here, for example, of the pharmacologically tolerable alkali metal, alkaline earth metal or earth metal salts of weak acids and the pharmacologically tolerable hydroxides and oxides of alkaline earth metals and earth metals. A base to be emphasized by way of example which may be mentioned is sodium carbonate.

Film coatings customary for sustained-release compositions which may be mentioned are membranes made of plastics having a low swelling power in water, in which small soluble particles are embedded, or in particular those swellable plastic membranes which contain a small proportion of a suitable salt which determines the permeability of the film coating.

Plastics suitable for the construction of the membranes are those which are water-insoluble and physiologically tolerable. Plastics having a low swelling power in water are understood for the purposes of the present invention as meaning, for example, those which absorb not more than 5% by weight of water in aqueous medium. For this, cellulose ethers and cellulose esters are regarded as particularly suitable. In addition, suitable plastics are also polymers such as polyvinyl chloride. Swellable plastics which may be mentioned are, in particular, copolymers of acrylic and methacrylic acid esters.

Small soluble particles which may be mentioned are, for example, lactose crystals, which are preferably employed in micronized form. The particle size is expediently less than 20  $\mu\text{m}$ , preferably less than 10  $\mu\text{m}$ . The ratio of plastic to soluble particles can be varied within wide limits. A weight ratio of plastic to soluble particles of approximately 2:1 to 1:3 is preferred. A weight ratio of 4:3 to 4:5 is particularly preferred.

Salts suitable for the swellable plastic membranes which may be mentioned are, for example, ammonium salts, in particular quaternary ammonium salts. In a particular embodiment of plastic membranes, some of the ester groups of a copolymer of acrylic and methacrylic acid esters are ester groups having quaternary ammonium structures. An example of such copolymers having quaternary ammonium

groups which may be mentioned is trimethylammonium methyl methacrylate chloride (e.g. Eudragit RL or Eudragit RS from Röhm).

The release time of the pyridin-2-ylmethylsulfinyl-1H-benzimidazoles can be controlled within a wide range by variation of the composition of the membrane and/or by variation of the layer thickness of the membrane. Thus, release is effected at an earlier time by lowering the layer thickness of the membrane, by increasing the proportion of soluble particles, by use of the soluble particles in a more coarse-grained form or, in the case of the swellable plastic membranes, by increasing the proportion of a suitable salt (e.g. higher proportion of quaternary ammonium groups in the copolymer of acrylic and methacrylic acid esters).

The application of the membrane to the tablet cores is carried out in a manner known per se, in particular by one of the customary spraying techniques. For this, a solution of the plastic or plastic mixture intended for the membrane is prepared in a solvent or in a solvent mixture or preferably an aqueous dispersion of the plastic or plastic mixture. The soluble, micronized particles are suspended in the solution before the spraying. If necessary, the suspension is stirred during the spraying in order to prevent settling of the suspended particles. In the case of the preferred procedure using aqueous dispersions, the salts responsible for the permeability of the plastic are already contained in the plastic itself in the form of quaternary ammonium groups. In the case of application of the membrane from an aqueous dispersion, it is also possible to work under alkaline conditions.

The membrane can contain the customary auxiliaries, such as plasticizers, wetting agents, colorants and antiadherents. Pharmacologically tolerable plasticizers such as, for example, polyethylene glycols, paraffins, glycerol or propylene glycol are suitable. Wetting agents may be necessary if the coating is to be dyed with dye lakes. Sorbitol fatty acid esters or salts of dioctylsulfosuccinic acid, for example, are suitable. Antiadherents which may be mentioned are, in particular, calcium stearate or talc.

With respect to the preparation and construction of the tablet cores reference is made, for example, to the embodiments in European Patent EP-B1-589 981.

The following examples of administration forms according to the invention explain the invention in greater detail without restricting it.

### Examples

#### **Example 1: Tablets**

##### **A. Tablet cores with 10 mg of active compound**

	Ingredients	per core
(a)	pantoprazole Na $\times$ 1.5 H <sub>2</sub> O	11.28 mg
(b)	sodium carbonate, anhydrous	2.50 mg
(c)	mannitol	10.68 mg
(d)	PVP, insoluble (Crospovidone)	12.50 mg
(e)	PVP 90	1.00 mg
(f)	calcium stearate	0.80 mg
	Total per core	38.75 mg

(a) is mixed with some of (b), (c) and (d). The remainder of (b) and (c) is added to the clear aqueous solution of (e) and adjusted to a pH of  $> 10$  using (b). Granulation is carried out in a fluidized bed granulator using this solution. The remainder of (d) and (f) is added to the dried granules and the granules are pressed in a suitable tablet machine.

##### **B. Coating**

	Ingredients	Initial weight	Coating per core
(g)	Eudragit RS 30 D	2400.00 g	4.876 mg
(h)	purified water	4800.00 g	
(i)	propylene glycol	144.00 g	0.975 mg
(j)	Ca stearate	21.60 g	0.146 mg
(k)	1 N NaOH	81.10 g	0.002 mg
	Total film coating	7446.70 g	6.000 mg

The ingredients are stirred to give a dispersion which is screened before processing. The dispersion is sprayed onto the cores obtained under A in a suitable apparatus.

The coating application of 6 mg per tablet core leads to a spontaneously commencing and complete release of active compound after 2 hours.

**Example 2: Combinations**

The following combinations of tablets according to the invention (prepared according to Example 1, comprising 10 mg of active compound, below "tablet E") and the known enteric tablets (prepared according to EP-B-589981, comprising 10 mg of active compound, below "tablet M") are, for example, conceivable, the tablets being dispensed into hard gelatin capsules of size 3:

- 1 tablet E + 1 tablet M
- 2 tablets E + 2 tablets M
- 3 tablets E + 1 tablet M
- 1 tablet E + 3 tablets M

Instead of the enteric tablets, the pellets prepared according to EP-B-589981 can also be used.

### Commercial applicability

The oral administration forms according to the invention can be employed for the treatment and prevention of all the diseases which are considered to be treatable or avoidable by the use of pyridin-2-ylmethylsulfinyl-1H-benzimidazoles. In particular, the oral administration forms according to the invention can be employed in the treatment of disorders of the stomach.

Surprisingly, sustained (i.e. more or less constant over a relatively long period) release behavior is not achieved using the oral administration forms according to the invention - despite the use of a customary sustained-release coating. On the contrary, initially no active compound at all is released over a certain period, the length of this period - as explained above - being controllable by the type and thickness of the membrane.

After expiry of the adjustable period, all of the active compound is then released within a very short space of time. Due to the dissolution of the particles embedded in the membrane, the membrane becomes porous or, due to the swelling of the permeable membrane, this becomes permeable and water penetrates into the core; as a result of this the tablet disintegrant begins to swell, and when the swelling pressure is sufficient in order to disintegrate the membrane, the active compound is released spontaneously and completely.

With the aid of the oral administration form according to the invention, it is thus possible to simulate an administration of active compound at a later time. As a result, the possibility is opened up of allowing a once daily administration instead of a twice daily administration of the active compound to begin by combining, for example, in one and the same administration form (e.g. in a capsule) two active compound forms whose release is different (e.g. a customary, enteric tablet and a tablet according to the invention).

The invention therefore further relates to the combination of an oral administration form according to the invention with a conventional (i.e. enteric-coated) administration form for pyridin-2-ylmethylsulfinyl-1H-benzimidazoles. "Combination" in this connection is understood as meaning the fixed or free combination.

In the fixed combination, both administration forms are present in a single dose unit (e.g. in a common tablet of outer conventional construction and inner core coated according to the invention, in a capsule comprising conventionally coated pellets and pellets according to the invention, or in particular in a capsule comprising two or more tablets, of which at least one corresponds to the specification according to the invention).

In the free combination, the two administration forms (that according to the invention and the conventional one) are present in separate dose units, which can be contained in a common packaging unit or in separate packaging units. In a common packaging unit, the different administration forms, for example, can be arranged in the form of capsules or tablets in rows lying next to one another in a blister pack. At the time indicated by the physician, the patient would in each case successively take a capsule or tablet from each row within a short length of time (in particular within 5 minutes).

Independently of whether a fixed or free combination is present, the compliance in the case of the combination according to the invention is in any case considerably greater than when two conventional administration forms have to be taken in a relatively large space of time (for example in the space of 3 to 12 hours).

The two-fold administration of active compound simulated by the fixed or free combination leads in a relatively large space of time (compared with the same dose of active compound as a single administration) to a smaller width of variation in the active compound blood levels in the patients and moreover to more rapid symptom relief.

In this connection, the fixed combination is preferred, particularly the combination of pellets according to the invention and conventional pellets and very particularly the combination of tablets according to the invention and conventional tablets in one capsule.

The treatment dose for an adult patient is, with respect to the pyridin-2-ylmethylsulfinyl-1H-benzimidazoles or their pharmaceutically tolerable salts, approximately 5 mg to 100 mg, in particular 10 mg to 80 mg, preferably 20 mg to 40 mg per day, calculated on the free acid. This treatment dose can be evenly or unevenly divided over the two administration forms in the combination according to the invention. A more or less equal division is preferred, e.g. 20 mg of the administration form according to the invention and 20 mg of the conventional (enteric-coated) administration form, in each case based on the free acid.

For their part, the oral administration forms according to the invention or the combinations according to the invention can in turn be combined with other medicaments, in particular with antimicrobial agents, such as are employed for the control of the bacterium *Helicobacter pylori* (*H. pylori*). Suitable antimicrobial agents for the control of the bacterium *H. pylori* which may be mentioned are bismuth salts [e.g. bismuth subcitrate, bismuth subsalicylate, ammonium bismuth(III) potassium citrate dihydroxide, bismuth nitrate oxide, dibismuth tris(tetraoxodialuminate)], but in particular  $\beta$ -lactam antibiotics, for example penicillins (such as benzylpenicillin, phenoxymethylpenicillin, propicillin, azidocillin, dicloxacillin, flucloxacillin, oxacillin, amoxycillin, bacampicillin, ampicillin, mezlocillin, piperacillin or azlocillin), cephalosporins (such as cefadroxil, cefaclor, cefalexin, cefixime, cefuroxime, cefatamet, cefadroxil, ceftibuten, cefpodoxime, cefotetan, cefazolin, cefoperazone, ceftizoxime, cefotaxime, ceftazidime,

- 9 -

cefamandol, cefepime, cefoxitin, cefodizime, cefsulodin, ceftriaxone, cefotiam or cefmenoxime) or other  $\beta$ -lactam antibiotics (e.g. aztreonam, loracarbef or meropenem); enzyme inhibitors, for example sulbactam; tetracyclines, for example tetracycline, oxytetracycline, minocycline or doxycycline; aminoglycosides, for example tobramycin, gentamicin, neomycin, streptomycin, amikacin, netilmicin, paromomycin or spectinomycin; amphenicols, for example chloramphenicol or thiamphenicol; lincomycins and macrolide antibiotics, for example clindamycin, lincomycin, erythromycin, clarithromycin, spiramycin, roxithromycin or azithromycin; polypeptide antibiotics, for example colistin, polymyxin B, teicoplanin or vancomycin; gyrase inhibitors, for example norfloxacin, cinoxacin, ciprofloxacin, pipemidic acid, enoxacin, nalidixic acid, pefloxacin, fleroxacin or ofloxacin; nitroimidazoles, for example metronidazole; or other antibiotics, for example fosfomycin or fusidic acid, where these antibacterially active substances - together with the oral administration forms according to the invention or with the combinations according to the invention - can be administered on their own or alternatively combined with one another. Combinations of antibacterially active substances which may be mentioned are, for example, amoxicillin plus metronidazole, clarithromycin plus metronidazole and amoxicillin plus clarithromycin.

PCT/EP99/05724

14.05.99

ANT 34 ABET

Patent claims

1. An oral administration form for pyridin-2-ylmethylsulfinyl-1H-benzimidazole and its salts, which comprises the active compound together with tablet disintegrants and is provided with a film coating which is customary per se for sustained-release compositions.
2. The administration form as claimed in claim 1, wherein the pyridin-2-ylmethylsulfinyl-1H-benzimidazole is omeprazole, esomeprazole, lansoprazole, rabeprazole, leminoprazole or nepaprazole.
3. The administration form as claimed in claim 1, wherein the pyridin-2-ylmethylsulfinyl-1H-benzimidazole is pantoprazole.
4. The administration form as claimed in claim 1, wherein the tablet disintegrant is Croscopvidone.
5. The administration form as claimed in claim 1, wherein the tablet disintegrant is Croscopvidone having a proportion in the tablet core of 20-35% by weight.
6. The administration form as claimed in claim 1, wherein the film coating is a copolymer of acrylic and methacrylic acid esters having quaternary ammonium structures.
7. A combination consisting of an administration form as claimed in claim 1 and an administration form of a pyridin-2-ylmethylsulfinyl-1H-benzimidazole having an enteric coating.
8. The administration form as claimed in claim 1 in combination with or for combined use with an antimicrobial agent.
9. The combination as claimed in claim 7 in combination with or for combined use with an antimicrobial agent.
10. The use of administration forms and combinations as claimed in one of claims 1 to 9 in the treatment of disorders of the stomach.



DECLARATION  
AND POWER OF ATTORNEY  
U.S.A.

ALL PATENTS, INCLUDING DESIGN  
FOR APPLICATION BASED ON PCT, PARIS CONVENTION;  
NON PRIORITY; OR PROVISIONAL APPLICATIONS

FOR ATTORNEY'S USE ONLY

ATTORNEY'S DOCKET NO.

As a below named inventor, I declare that my residence, post office address and citizenship are stated below next to my name, the information given herein is true, that I believe that I am the original, first and sole inventor (if only one name is listed at 201 below), or a first and joint inventor (if plural inventors are named below at 201-203, or on additional sheets attached hereto) of the subject matter which is claimed and for which patent is sought on the invention entitled:

Oral administration form for pyridin-2-ylmethylsulfanyl-1H-benzimidazoles

which is described and claimed in

☒ PCT International Application No. PCT/EP99/05724

filed 7 August 1999

☐ the attached specification

☐ the specification in application  
(if applicable) and

filed

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above. I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56

I hereby claim foreign priority benefits under Title 35, United States Code, §119(a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application Number(s)	Country	Foreign Filing Date (Day/Month/Year)	Priority claimed Yes	Priority claimed No
No. 98115141.8	European Application	12/08/1998	X	

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

Application No.

Filing date:

Application No.

Filing date:

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application

(Application Serial No.)

(Filing Date)

(Status: patented, pending, abandoned)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorneys (Registration No.) to prosecute this application, receive and act on instructions from my agent, and transact all business in the Patent and Trademark Office connected therewith HARVEY B JACOBSON JR. (20,851); D. DOUGLAS PRICE (24,514); JOHN CLARKE HOLMAN (22,769); MARVIN R. STERN (20,640); MICHAEL R. SLOBASKY (26,421); JONATHAN L. SCHERER (29,851); IRWIN M. AISENBERG (19,007); WILLIAM E. PLAYER (31,409)

SEND CORRESPONDENCE TO

**JACOBSON, PRICE, HOLMAN & STERN**  
PROFESSIONAL LIMITED LIABILITY COMPANY  
400 SEVENTH STREET N.W.  
WASHINGTON, DC, 20004

DIRECT TELEPHONE CALLS TO:

(please use Attorney's Docket No.) (202) 638-6666

**JACOBSON, PRICE, HOLMAN & STERN**  
PROFESSIONAL LIMITED LIABILITY

\*Inventor(s) name must include at least one unabbreviated first or middle name.

201	FULL NAME OF INVENTOR *	FAMILY NAME	GIVEN NAME	MIDDLE NAME		
	DIETRICH		Rango			
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP		
	Konstanz	Germany	DEX	Germany		
202	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE	
	Im Tiergarten 16		Konstanz	Germany	78465	
	FULL NAME OF INVENTOR *	FAMILY NAME	GIVEN NAME	MIDDLE NAME		
	NEY		Hartmut			
203	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP		
	Konstanz		Konstanz	Germany		
	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE	
	Peter-Thum-Str. 46		Konstanz	Germany	DEX	78464
208	FULL NAME OF INVENTOR *	FAMILY NAME	GIVEN NAME	MIDDLE NAME		
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP		
209	POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE	

I further declare that all statements made herein of my own knowledge are true and that all statement made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of Title 18 of the United States Code; and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201 *	SIGNATURE OF INVENTOR 202 *	SIGNATURE OF INVENTOR 203 *
DATE Jan 24, 2001	DATE Jan 24, 2001	DATE

☐ Additional inventors are named on separately numbered sheets attached hereto.  
© JPH&S 1995 8/95; 3/96; 5/98 (COPYING WITHOUT DELETIONS PERMITTED)

## Abstract

The invention relates to an oral administration form for pyridin-2-ylmethylsulfinyl-1H-benzimidazoles and their salts, which comprises the active compound together with tablet disintegrants and is provided with a film coating customary per se for sustained-release compositions.

Publ. No. 2 000 000 000